REMARKS

In view of the above amendments and the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow Claims 1-15, the only claims pending and currently under examination in this application.

The claims have been amended to specify that the solution phase product produced by the methods is made up of single stranded nucleic acids. Support for this amendment can be found in the specification where linear PCR, SDA and in vitro protocols are described, which all produce single stranded nucleic acids. Accordingly, this amendment introduces no new matter and its entry by the Examiner is respectfully requested.

Objection under 35 U.S.C. § 132 and rejection under 35 U.S.C. § 112, first paragraph

The Final Rejection maintains the Examiner's position that the amendment filed September 3, 2002 contains new matter pursuant to 35 U.S.C. § 132 and does not comply with the requirements of 35 U.S.C. § 112, 1st ¶.

As summarized in the Applicants' prior submission, the issue driving this objection and rejection is whether or not a primer extension reaction that produces *a solution phase* product comprising a mixture of nucleic acids of differing sequence is adequately described in the specification as filed. In other words, would one of skill in the art determine that the specification supports a *solution phase* of nucleic acids of differing sequence?

In support of the position that the subject matter of the amended claims was adequately described in the application as filed, and, accordingly, the amendment did not introduce new matter into the disclosure of the application, the Examiner was directed to the specification beginning at page 10, line 25, where three different representative primer extension reactions are discussed, i.e., linear PCR, strand

displacement amplification and in vitro transcription, where all three of these protocols as described in the specification produce a solution phase product.

First, the above amendment removing the term "primer extension" should obviate this rejection.

Furthermore, the Examiner discounts the Applicants' position in part by arguing that PCR requires use of two different primers, which is an element excluded by the claims and therefore citing PCR cannot support the Applicants' position. However, linear PCR does not require two different primers, but only a single primer. In linear PCR, only one strand is amplified because only one primer is employed through multiple cycles, such that one does not obtain geometric amplification, but only linear amplification. As the Applicants' cited to linear PCR, and not just PCR, in their previous arguments, and linear PCR only employs one primer, the portion of the specification describing the linear PCR embodiment does describe a reaction that produces a solution phase product.

Likewise, the Examiner also discounts the Applicants' position in part by arguing that SDA requires use of two different primers, which is an element excluded by the claims and therefore citing SDA cannot support the Applicants' position. However, the SDA protocol described by in the specification does not require two different primers, but only a single primer. In the SDA protocol described by the Applicants in the specification, only a single primer is employed and extended, and only the primer extended strand is knicked and displaced. As the Applicants' cited to an SDA protocol that only employs one primer, the portion of the specification describing the SDA embodiment does describe a reaction that produces a solution phase product.

Furthermore, the Examiner discounts the Applicants' position in part by arguing that in vitro transcription does not require a primer and therefore citation to this representative embodiment cannot support the Applicants' position. However, in vitro transcription does require a double-stranded promoter. The double-stranded promoter is recognized by the RNA polymerase employed for transcription; the RNA

polymerase then transcribes in a 5' to 3' manner, using the 3' to 5' strand extending from the double-stranded recognition site as a template. In most cases, the extending 3' to 5' template strand is part of a DNA duplex. However, it is well-known to the art (Milligan, J. F., Groebe, D. R., Witherell, G. W. & Uhlenbeck, O. C. (1987) Nucleic Acids Res 15, 8783-98) that a single-stranded 3'-to-5' template strand is transcribed just as efficiently as a double-stranded template, provided that the full double-stranded promoter region is present. The transcription product is observed in solution. Recent work on the structure of RNA polymerases rationalizes this result: RNA polymerases physically segregate the product RNA strand from the template DNA strand via structures that physically separate the strands. Accordingly, the Applicants' in vitro transcription protocol described in the specification does describe a reaction that produces a solution phase product.

It is respectfully submitted that the above discussion successfully rebuts the Examiner's position in maintaining the objection and rejection because PCR and SDA do not require the use of two primers and the in vitro transcription protocol described by the Applicant in the specific does include an in vitro transcription step known to produce solution product and therefore also supports the claim language.

Based on the foregoing, the Applicants respectfully submit that one of skill in the art would unequivocally find adequate description of "a reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence" in the application as originally filed. Accordingly, the phrase "a reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence" cannot represent new matter.

Since the phrase "a reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence" does not represent new matter, the objection to the amendment filed September 3, 2002, under 35 U.S.C. § 132 and the rejection of claims 1-15 under 35 U.S.C. § 112, first paragraph, may be withdrawn.

Rejection of Claims 1-15 under 35 U.S.C. § 102(e) over Wolber

Claims 1-15 have been rejected under 35 U.S.C. § 102(e) as being anticipated by Wolber. As evidence by the enclosed declaration of Paul Wolber declaring that he conceived and invented the subject matter disclosed but not claimed in the cited patent that is the subject of the claims of the present application, this rejection may be withdrawn.

Rejection of Claims 1-4 under 35 U.S.C. § 102(b) over Bulyk

Claims 1-4 have next been rejected under 35 U.S.C. § 102(b) as being anticipated by Bulyk. In making this rejection, the Examiner asserts that Bulyk teaches in part "separating said mixture from said template array." Following entry of the above amendment, the claims are limited to methods that produce a solution phase of single stranded nucleic acids. Bulyk teaches a method of cleaving surface immobilized double stranded (ds) structures using restriction endonucleases, which produces a mixture of ds nucleic acids. As such, Bulyk does not anticipate the claims and this rejection may be withdrawn.

Rejection of Claims 5-6 and 8-9 under 35 U.S.C. § 103(a) over Bulyk

Claims 5-6 and 8-9 have next been rejected under 35 U.S.C. § 103(a) as being obvious over Bulyk. In making this rejection, the Examiner asserts that Bulyk teaches in part "separating said mixture from said template array." Following entry of the above amendment, the claims are limited to methods that produce a solution phase of single stranded nucleic acids. Bulyk teaches a method of cleaving surface immobilized ds structures using restriction endonucleases, which produces a mixture of ds nucleic acids. As such, Bulyk does not teach or suggest a method that produces ss nucleic acids, and therefore does not make these claims obvious. Accordingly, this rejection may be withdrawn.

Rejection of Claims 7 under 35 U.S.C. § 103(a) over Bulyk in view of Dattagupta

Claim 7 has next been rejected under 35 U.S.C. § 103(a) as being obvious over Bulyk in view of Dattagupta. In making this rejection, the Examiner asserts that Bulyk teaches in part "separating said mixture from said template array." Following entry of the above amendment, the claims are limited to methods that produce a solution phase of single stranded nucleic acids. Bulyk teaches a method of cleaving surface immobilized ds structures using restriction endonucleases, which produces a mixture of ds nucleic acids. As such, Bulyk does not teach or suggest a method that produces ss nucleic acids, and therefore does not make these claims obvious. As Dattagupta has been cited solely for the element of an RNA polymerase, this secondary reference cannot make up the above described fundamental deficiency in Bulyk. Accordingly, this rejection may be withdrawn.

Rejection of Claims 10 to 15 under 35 U.S.C. § 103(a) over Bulyk in view of Cantor

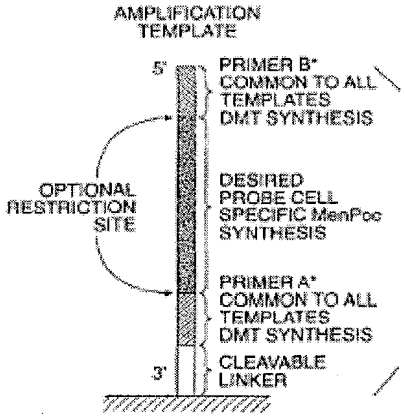
Claims 10-15 have next been rejected under 35 U.S.C. § 103(a) as being obvious over Bulyk in view of Cantor. In making this rejection, the Examiner asserts that Bulyk teaches in part "separating said mixture from said template array." Following entry of the above amendment, the claims are limited to methods that produce a solution phase of single stranded nucleic acids. Bulyk teaches a method of cleaving surface immobilized ds structures using restriction endonucleases, which produces a mixture of ds nucleic acids. As such, Bulyk does not teach or suggest a method that produces ss nucleic acids, and therefore does not make these claims obvious. As Cantor has been cited solely for the teaching of the use of the solution phase product in target generation, this secondary reference cannot make up the above described fundamental deficiency in Bulyk. Accordingly, this rejection may be withdrawn.

Rejection of Claims 1-6 and 8-9 under 35 U.S.C. § 103(a) over Lipshutz in view of Bulyk

Claims 1-6 and 8-9 have next been rejected under 35 U.S.C. § 103(a) as anticipated by Lipshutz (USPN 6,280,950) in view of Bulyk, assertedly because Lipshutz describes a primer extension reaction performed upon an array of nucleic acid probes that teaches all of the elements of the claimed methods but for the use of 5' variable domain, which is assertedly taught by Bulyk.

Lipshutz discloses a method for producing a mixture of nucleic acids involving an array of nucleic acid probes. The composition of Lipshutz probes is described in great detail in column 2 line 66 to column 3 line 35 and summarized in the first panel of Fig. 1 of the Lipshutz disclosure. This panel of Fig. 1 of the Lipshutz reproduced here for the Examiner's convenience.

First panel of Figure 1 of Lipshutz (USPN 6,280,950):



As can be seen from the figure, the Lipshutz probes contain regions at the 5' and 3' ends of the probes that are called "PRIMER B* COMMON TO ALL TEMPLATE DMT SYNTHESIS" and "PRIMER A* COMMON TO ALL TEMPLATE DMT SYNTHESIS", respectively. These regions are homologous to the constant regions of the probes recited in the instant claims. These probes are the only probes on Lipshutz' array, and, as such, Lipshutz only teaches an array containing probes containing constant regions at their 5' ends.

Even in view of Bulyk, one of skill in the art would not be motivated to modify the Lipshutz array to contain probes that have variable domains at their 5' ends since all of Lipshutz primer extension methods involve amplification reactions that require the presence of two constant domains as primer sites (e.g. non-linear PCR

amplification). A variable domain placed on the 5' end of Lipshutz probes would not be amplifiable using Lipshutz' methods, and, as such, one of skill in the art would lack motivation to change Lipshutz' methods to teach the claimed method.

Bulyk fails to provide any such motivation because Bulyk only cleaves the ds nucleic acids to confirm that primer extension reactions were complete, and therefore would not be looked to by one of skill in the art as motivation to modify the Lipshutz method to use a 5' variable domain. Furthermore, if one were to modify Lipshutz in view of Bulyk, one would also have to include a cleavage step as taught by Bulyk, where the entire surface immobilized duplex structure is cleaved from the surface, which one negate the workability of Lipshutz' method.

Because the Lipshutz fails to teach an array containing probes that have constant domains at their 5' ends and one of skill in the art would not be motivated by Bulyk to modify Lipshutz to include a 5' variable domain, Claims 1-6 and 8-9 are not obvious over Lipshutz in view of Bulyk and this rejection may be withdrawn.

Rejection of claim 7 under 35 U.S.C. § 103

Claim 7 has been rejected under 35 U.S.C. § 103(a) as being obvious over Lipshutz and Bulyk and further in view of Dattagupta.

As established above, the combined teaching of Lipshutz and Bulyk is deficient in that it does not teach an array of probes containing variable domains at their 5' ends. This deficiency is not made up by Dattagupta's RNA polymerase, and cannot be met by knowledge available to one of skill in the art. As such, the combination of Lipshutz and Bulyk in view of Dattagupta cannot render the subject matter of Claim 7 obvious. Accordingly, this rejection may be withdrawn.

Rejection of Claims 10-15 under 35 U.S.C. § 103 over Lipshutz in view of Bulyk and further in view of Cantor

Claims 10-15 have been rejected under 35 U.S.C. § 103(a) as being obvious over Lipshutz and Bulyk in view of Cantor.

Each of Claims 10-15 involves the method of producing a mixture of nucleic acids recited in Claim1. As such, each of Claim 10-15 involves an array containing

probes having variable domains at their 5' ends. Claims 10-13 further involve a target generation step in which target nucleic acids are produced from an mRNA sample. The target generation step requires a variable domain at the 5' end of the probes for a target to be generated.

As established above, the combined teaching of Lipshutz and Bulyk is deficient in that it fails to make obvious the claimed protocols of using an array containing probes that have variable domains at their 5' ends. As previously established above and in the Applicants' previous response, Lipshutz strongly teaches away from using probes that have a variable domain at their 5' ends since Lipshutz' primer extension methods involve amplification reactions that require the presence of two constant domains acting as primer sites, and Bulyk is not concerned with making product nucleic acids for use in another application.

Cantor's methods of employing Lipshutz' mixture of nucleic acids fails to make up for the fundamental Lipshutz/Bulyk deficiency. As such, Lipshutz and Bulyk in combination with Cantor fails to teach or suggest the claimed invention and this rejection may be withdrawn.

CONCLUSION

The applicant respectfully submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone Gordon Stewart at 650 485 2386. The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-1078.

Respectfully submitted,

Date: 8.18.03

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